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Hypermobile Ehlers–Danlos syndrome and pregnancy

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Abstract

Ehlers–Danlos syndromes are a clinically and genetically heterogeneous group of rare inherited connective tissue disorders. Hypermobile Ehlers–Danlos syndrome is one of the common types and not infrequently encountered in pregnancy. While, in the majority of women with hypermobile Ehlers–Danlos syndrome, the pregnancy is uncomplicated, it is important to be aware of the condition in view of potential complications such as recurrent joint dislocations and history of surgical joint stabilization procedures, secondary autonomic pain and postural orthostatic tachycardia syndrome. Increased awareness of the condition and a multi-disciplinary approach to the management of these women in pregnancy result in good outcome for the mother and the baby. We report the clinical characteristics and outcome of pregnancies in eight women with hypermobile Ehlers–Danlos syndrome and present a review of the literature with particular reference to management in a pregnant woman with joint hypermobility syndrome.

Keywords

High-risk pregnancy, maternal-fetal medicine

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Introduction

Ehlers–Danlos syndromes (EDS) are a clinically and genetically heterogeneous group of rare inherited connective tissue disorders characterized by joint hypermobility, skin hyperextensibility and tissue fragility. Six subtypes have been delineated that have been widely used as the standard for clinical diagnosis of EDS[1,2] (Table 1).

The 2017 International Classification for the EDS recognizes 13 subtypes.[3] It included all phenotypes that present the basic clinical hallmarks of EDS, that is joint hypermobility, skin hyperextensibility and tissue fragility and the hypermobile type was redefined. The diagnosis of hypermobile Ehlers–Danlos syndrome (hEDS) remains clinical as there is yet no reliable or appreciable genetic aetiology to test for in the vast majority of patients (Table 2). As we started our work prior to the 2017 classification, our work is based on the previously used Brighton criteria (Box 1).

We report pregnancies in eight women with hEDS, detailing the clinical characteristics, and present a review of the current literature. While pregnancy and childbirth is often a completely normal experience for women with hEDS, it is important to be aware of a number of complications that can arise. Increased awareness of this condition and the potential problems that can arise can alert a clinician to managing these pregnancies effectively with appropriate interventions when required.

Summary of cases

Table 3 summarizes the obstetric history, clinical symptoms and outcome of pregnancies. All women had hypermobility of one or more joints. Most women had chronic pain requiring regular analgesia and input from the pain management team. The majority experienced pelvic girdle pain in pregnancy, which was remarkably early in onset and required physiotherapy input. One patient suffered from severe gastro-intestinal hypomotility symptoms and required percutaneous endoscopic gastrostomy (PEG) feeds; the hypomotility worsened in pregnancy requiring more frequent PEG feeds. Two women had symptoms of gastro-oesophageal reflux from hiatus hernia. Caesarean section was the most common mode of delivery (six out of eight cases); the predominant reasons for caesarean birth were obstetric indications. These included previous caesarean section (along with maternal request) in three women, poor progress in labour in one woman and placental abruption at 31 weeks in one woman. One woman declined vaginal delivery as she was anxious about her recurrent hip joint dislocations and obstetric cholestasis; caesarean section was done at maternal request.

Although the majority had a definite history of resistance to local anaesthetics (previous dental procedures), regional blockade for pain relief in labour/caesarean section was found to be effective in these women. One woman required more frequent top-up with local anaesthetics for epidural for effective pain relief in labour.

A multi-disciplinary approach was adopted in the management of these women in pregnancy, including anaesthetic consultation and where required referral to the pain management team, physiotherapy and cardiology.

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Table 1. Classification of Ehlers–Danlos syndrome (Villefranche Nosology).

Ehlers–Danlos syndrome – Type	Inheritance	Clinical features	Reported pregnancy-related problems
Classical (Type 1 and 2)	AD	Skin hyperextensibility, easy bruising, tissue friability, joint hypermobility	Preterm labour, PPROM, perineal trauma, PPH
Hypermobility (Type 3)	AD	Generalised joint hypermobility, recurrent joint dislocation/pain, mild cutaneous manifestations	PoTS, preterm labour, PPROM, perineal trauma, PPH
Vascular (Type 4)	AD	Facial dysmorphism, thin translucent skin, poor wound healing, excessive bruising/haematomas, vascular rupture and intestinal perforation	Mortality around 12%. Risk of arterial or uterine rupture, PPH requiring hysterectomy
Kyphoscoliotic (Type 6)	AR	Soft velvety skin, poor scarring, joint-laxity, dislocations and kyphosis, ocular fragility, vascular rupture, mitral valve prolapse	Miscarriage, preterm labour, PROM, arterial rupture
Arthrochalasia (Type 7A-B)	AD	Severe generalised joint hypermobility and dislocations, floppy infants, scoliosis, mild skin features	
Dermatosparaxis (Type 7C)	AD	Severe skin manifestations – fragility, bruising, poor scarring, visceral rupture	PPROM and preterm labour, lacerations and fractures at birth

AD: autosomal dominant; AR: autosomal recessive; PPROM: preterm prelabour rupture of membranes; PPH: postpartum haemorrhage; PoTS: postural orthostatic tachycardia syndrome.
Inheritance pattern, clinical features and pregnancy-related problems (adapted from (1,2)).

Discussion

This review focuses on hEDS. This is the benign form and accounts for about 35% of cases of EDS. The main clinical features are joint hypermobility/laxity, joint pains and recurrent joint dislocations/subluxations occurring spontaneously or with minimal trauma, which can be acutely painful.[4,5] Hyperextensibility of the skin, easy bruising, psychological dysfunction, psychosocial impairment and emotional problems are common. Gastrointestinal and cardiovascular systems are sometimes involved. Hypermobile EDS has an autosomal dominant pattern of inheritance. Beighton developed a scoring system based on joint hypermobility that has been deployed in epidemiological studies (Box 1). Brighton criteria use this Beighton score along with clinical symptoms for the diagnosis of joint hypermobility syndrome (JHS), which is entirely clinical.[6] Table 4 summarizes the diagnostic workup used based on Brighton Criteria in our patients.

Complications of hEDS in pregnancy

Overall, pregnancy is well tolerated in hEDS. Possible complications are mainly attributable to joint hypermobility, skin and tissue fragility and abnormal collagen in blood vessels. It is generally a benign condition and the majority of women tolerate pregnancy well with good outcomes. The following review describes the potential complications of hEDS.

First trimester

No complications have been specifically reported as pertaining to the first trimester. Increased mucosal fragility can lead to spontaneous epistaxis and gingival bleeding predisposing to gingival inflammation and infections, caries and loss of teeth. Hypermobile EDS contributes to an increased tendency to joint subluxations, sprains, fasciitis and synovitis. Repeated dislocations and sprains may either worsen the joint instability or cause progressive joint stiffness. The physiological changes in pregnancy can aggravate the joint symptoms.

Mild cardiovascular involvement may be found in JHS patients. Minor structural anomalies mostly involving tricuspid/mitral valves, increased lung volumes, increased tendency of upper and lower airways to collapse are amongst other features. Careful antenatal assessment at booking will enable appropriate management during pregnancy and delivery.

Gastro-intestinal involvement is common including delayed gastric emptying, sluggish bowel motility, reflux, gastritis, irritable bowel syndrome and constipation/diarrhoea. These can worsen in pregnancy. Underlying mechanisms seem to be poor fixation to adjacent structures leading to hernias and visceroptosis, and gut hypotonia and hypomobility.[7] Rectal hyposensitivity can cause constipation.[8] Some cases require PEG feeds for long-term nutritional support, in which a tube is passed into a patient's stomach through the abdominal wall, to provide a means of feeding when oral intake is not adequate.

Second trimester

Skin hyperextensibility is a known feature of JHS. It was thought that preterm labour was a well-recognized complication of pregnancies with JHS and this was commonly preceded by rupture of membranes (ROM); this is attributed to the fetus inheriting the condition, the fragility of fetal tissues manifested in chorionic membranes leading to premature ROM.[9] More recent data do not support this association.[10]

Table 2. 2017 International Classification-Diagnostic criteria for hEDS.

2017 International Classification-Diagnostic criteria for hEDS (Table 2, adapted from 3)
The clinical diagnosis of hEDS needs the simultaneous presence of criteria 1, 2 and 3.
Criterion 1: GJH
The Beighton scoring system. Each joint is measured using a goniometer and each side is scored independently as outlined.[4]
(A) With the palm of the hand and forearm resting on a flat surface with the elbow flexed at 90°, if the metacarpal-phalangeal joint of the fifth finger can be hyperextended more than 90° with respect to the dorsum of the hand, it is considered positive, scoring 1 point.
(B) With arms outstretched forward but hand pronated, if the thumb can be passively moved to touch the ipsilateral forearm, it is considered positive scoring 1 point.
(C) With the arms outstretched to the side and hand supine, if the elbow extends more than 10°, it is considered positive scoring 1 point.
(D) While standing, with knees locked in genu recurvatum, if the knee extends more than 10°, it is considered positive scoring 1 point.
(E) With knees locked straight and feet together, if the patient can bend forward to place the total palm of both hands flat on the floor just in front of the feet, it is considered positive scoring 1 point. The total possible score is 9.
The Committee on behalf of the International Consortium on the Ehlers–Danlos Syndromes proposes 6 for pre-pubertal children and adolescents, 5 for pubertal men and women up to the age of 50, and 4 for those >50 years of age for hEDS.
Criterion 2: Two or more among the following features (A–C) MUST be present (for example, A and B; A and C; B and C; A, B and C)
Feature A: Systemic manifestations of a more generalized connective tissue disorder (a total of five must be present)
1. Unusually soft or velvety skin
2. Mild skin hyper extensibility
3. Unexplained striae such as striae distensae or rubrae at the back, groins, thighs, breasts and/or abdomen in adolescents, men or prepubertal women without a history of significant gain or loss of body fat or weight. Bilateral piezogenic papules of the heel
4. Recurrent or multiple abdominal hernia(s) (e.g. umbilical, inguinal, crural)
5. Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS
6. Pelvic floor, rectal and/or uterine prolapse in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition
7. Dental crowding and high or narrow palate
8. Arachnodactyly, as defined in one or more of the following: (i) positive wrist sign (Steinberg sign) on both sides; (ii) positive thumb sign (Walker sign) on both sides
9. Arm span-to-height 1.05
10. MVP mild or greater based on strict echocardiographic criteria
11. Aortic root dilatation with Z-score > þ2
Feature B: Positive family history, with one or more first-degree relatives independently meeting the current diagnostic criteria for hEDS.
Feature C: Musculoskeletal complications (must have at least one):
1. Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
2. Chronic, widespread pain for 3 months
3. Recurrent joint dislocations or frank joint instability, in the absence of trauma (a or b). (a) Three or more atraumatic dislocations in the same joint or two or more atraumatic dislocations in two different joints occurring at different times. (b) Medical confirmation of joint instability at two or more sites not related to trauma
Criterion 3: All the following prerequisites MUST be met
1. Absence of unusual skin fragility, which should prompt consideration of other types of EDS
2. Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. In patients with an acquired connective tissue disorder (e.g. lupus, rheumatoid arthritis, etc.), additional diagnosis of hEDS requires meeting both Features A and B of Criterion 2. Feature C of Criterion 2 (chronic pain and/or instability) cannot be counted towards a diagnosis of hEDS in this situation.
3. Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders (e.g. myopathic EDS, Bethlem myopathy), other HCTD (e.g. other types of EDS, Loeys–Dietz syndrome, Marfan syndrome) and skeletal dysplasias (e.g. OI). Exclusion of these considerations may be based upon history, physical examination and/or molecular genetic testing, as indicated.

hEDS: hypermobile Ehlers–Danlos syndrome; GJH: generalized joint hypermobility; EDS: Ehlers–Danlos syndrome; MVP: mitral valve prolapse; HCTD: Heritable connective tissue disorder; OI: osteogenesis imperfecta.

Third trimester and delivery

The articulation problems necessitate extra physiotherapy input and care during positioning in labour. Widespread musculoskeletal pain and muscle weaknesses are recognized features, which causes excessive fatigue during pregnancy. These symptoms revert to pre-pregnancy state in the postnatal period.

Women with JHS may experience quick or precipitate labour with an increased risk of perineal lacerations due to increased tissue fragility.[11] Delivery through the perineum is described. Difficult forceps delivery should be avoided where possible. Traumatic and atonic postpartum haemorrhage can result from increased capillary fragility and defective connective tissue. No coagulation abnormalities have been reported in JHS.[12]

Delayed wound healing and atrophic scars are not uncommon. This has implications in pregnancy including healing of perineal or caesarean wounds.[7] Delayed complications include wound dehiscence and incisional hernia. Increased tissue and capillary fragility can cause easy bruising, spontaneous ecchymosis and haematomas and can potentially make surgery difficult, therefore gentle tissue handling during surgery in these women is advised.

Box 1 Diagnosis of joint hypermobility syndrome.[6]

Brighton criteria

Major

- Beighton score of ≥4, either now or in the past
- Joint pain in ≥4 joints for ≥3 months

Minor

- Beighton score 1–3 (or 0–3 if over 50 years)
- Joint pain for longer than 3 months in one to three joints
- Back pain, spondylosis or spondylolisthesis for ≥3 months
- Dislocating/subluxating >1 joint or the same joint more than once
- Having ≥3 injuries to soft tissues, such as tenosynovitis or bursitis
- Marfanoid habitus
- Abnormal skin, such as thin/stretchy skin
- Eye symptoms, such as droopy eyelids or myopia
- Varicose veins
- Hernia
- Rectal or uterine prolapse

Beighton score

- Passive apposition of thumb to the flexor aspect of forearm (one point for each hand)
- Passive dorsiflexion of the fifth finger >90° (one point for each hand)
- Hyperextension of the elbow >10° (one point for each hand)
- Hyperextension of the knees >10° (one point for each leg)
- Forward flexion of the trunk with the knees extended and palms resting flat on the floor

According to the Brighton criteria, JHS may be diagnosed if you have:

- Two major criteria
- One major criteria and two minor criteria
- Four minor criteria
- Two minor criteria and a close relative, such as a parent, who has been diagnosed with JHS

Pelvic organ prolapse can complicate the postpartum period and has been reported to occur in 15% of women.[7,13]

Anaesthetic concerns

Analgesia and duration of analgesia from local anaesthetics can be significantly reduced in patients with hEDS.[14] This fact has to be taken into consideration if women need perineal local anaesthetic infiltration for episiotomy. The exact mechanism of resistance to local anaesthetics in women with JHS is poorly understood; a double dose of the local anaesthetic may be effective in these patients. There are also concerns with the effectiveness of epidural analgesia for pain relief in labour; more frequent top-ups may be required. For caesarean section, combined spinal epidural (CSE) that allows top-ups to be given as required is preferred to single shot spinal analgesia.

Temporo-mandibular joint dysfunction can cause masticatory dysfunction, clicks and articular locks. Intubation and airway management may prove difficult, particularly in women with a history of temporomandibular joint (TMJ) dysfunction/dislocation and instability of cervical spine. Collapse of fibro-elastic tissues and mucosal fragility may add to the difficulty. The anaesthetic management should include airway assessment . In women with TMJ symptoms/dislocation, Wiesman noted an increased possibility of difficult airway management and intubation in pregnant women compared to the general population.[4]

Table 3. Clinical features and pregnancy outcome.

	Previous obstetric history		Clinical symptoms/complications						Index pregnancy (pregnancy outcome)				
Case no.	Parity	Quick labour	History of joint dislocation	Chronic pain	Gastro-intestinal symptoms	Postural orthostatic tachycardia syndrome	Resistance to local anaesthetics	Pelvic girdle pain	Threatened preterm labour	Preterm labour	Mode of delivery/ gestational age	Neonatal birth weight centile
1	1	–	✓	✓	–	–	✓	✓	–	–	Caesarean section/39 weeks	90th
2	2	✓	✓	✓	–	–	✓	✓	✓	–	Vaginal delivery/38 weeks	40th
3	3	–	✓	✓	–	–	✓	✓	✓	✓	Caesarean section/31 weeks Placental Abruption	25th
4	1	✓	✓	✓	✓	✓	✓	✓	✓	✓	Vaginal delivery/29 weeks	50th
5	2	–	✓	✓	✓	–	–	✓	–	–	Caesarean section/39 weeks	50th
6	1	–	✓	✓	–	–	–	✓	–	–	Caesarean section/39 weeks	60th
7	1	–	✓	–	–	–	–	–	✓	–	Caesarean section/38 weeks	12th
8	0	–	✓	✓	✓	–	✓	✓	✓	–	Caesarean section/38 weeks	11th

Table 4. Diagnostic workup based on Brighton criteria.

Case number	Criteria used	Major criteria	Minor criteria
1	Two minor and a close relative		Abnormal skin, recurrent shoulder dislocation and family history
2	One major and two minor	Joint pain >4 joints for >3 months	Recurrent knee dislocation and abnormal skin
3	One major and two minor	Joint pain >4 joints for >3 months	Back pain >3 months and recurrent hip dislocation
4	One major and two minor	Joint pain >4 joints for >3 months	Recurrent shoulder dislocation and abnormal skin
5	One major and two minor	Beighton score >4	Back pain >3 months and hernia
6	Four minor		Abnormal skin, family history, joint pain >3 months in 2 joints and >1 joint dislocation
7	Four minor		Recurrent hip dislocation, shoulder pain >3 months, abnormal skin and Beighton score 2
8	Four minor		Recurrent temporomandibular joint dislocation, knee pain >3 months, abnormal skin and hernia

Associated conditions

Autonomic pain

Chronic pain including abdominal/pelvic pain is by far the commonest and most serious disabling complication of this condition. Severity of pain neither correlates with the degree of joint instability nor is explained by physical and radiologic findings and can be worsened during pregnancy as noted in one woman who was on gabapentin, duloxetine and morphine patches. This was managed in close consultation with the pain management team. Patients with JHS are often already diagnosed with chronic fatigue syndrome and fibromyalgia. Associated manifestations include sleep disturbance and emotional or behavioural distress.[5] Management of pain includes physiotherapy support, use of medications tailored to the symptoms and needs of the patient and anaesthetic/steroid injections for localized joint pain. Some situations may require orthopaedic surgical interventions and even surgical nerve root destruction but are often deferred until after delivery.

Postural tachycardia syndrome

Postural orthostatic tachycardia syndrome (PoTS) is a recognized complication of JHS and is due to cardiovascular autonomic dysfunction.[15,16] This is mostly seen in young women and as such can pose an additional problem in pregnancy/delivery.

PoTS is characterized by marked increase in heart rate of 30 beats per minute (bpm) or greater occurring within 10 min of head-up tilt or standing, or a heart rate while upright of >120 bpm, but without orthostatic hypotension.[15] These patients experience sudden onset of symptoms like dizziness, light-headedness, visual disturbances, loss of consciousness, shortness of breath and palpitations. Non-specific symptoms like fatigue and lethargy with change of posture occurring with upright posture and relieved on lying flat can sometimes be noted. Migraine is a common associated condition in JHS patients with PoTS as opposed to other conditions leading to PoTS.[17]

A possible mechanism explaining the occurrence of PoTS in women with JHS include – autonomic dysfunction resulting in (a) peripheral venous pooling in the legs while standing due to peripheral denervation;[18] (b) impaired storage and release of norepinephrine in nerve endings; this appears to be more pronounced in the legs than arms;[19] (c) failure of activation of the normal aortic baroreceptor reflex to maintain blood pressure and cerebral perfusion, and therefore requiring excessive tachycardia to maintain blood pressure.[20] The symptoms are usually unmasked or worsened by stimuli including stress, dehydration, exertion, food indigestion and pregnancy due to vasodilatation and redistribution of intravascular fluid volume.

The hemodynamic changes in pregnancy and stress and pain of labour often exacerbate the symptoms in JHS complicated with PoTS. It is essential, however, to exclude other causes including endocrine and cardiac causes. PoTS may have a variable clinical course in pregnancy; in general, those who were asymptomatic prior to pregnancy are less likely to develop severe symptoms. Several non-pharmacological measures can make significant improvement to these symptoms; these include avoiding dehydration, adequate salt and water intake, small frequent meals, judicious exercising and avoidance of alcohol and medications like nifedipine. To combat the lower limb peripheral vasodilatation, elastic stockings should be considered in pregnancy. Symptomatic women should also be advised to avoid prolonged recumbency and high environmental temperatures; head up tilt at night may also be beneficial. Most of the pharmacologic agents advocated for management of this condition are unsafe in pregnancy and in the event of requiring a medication to control symptoms, expert advice is to be sought.

Normal vaginal delivery can be encouraged in women with PoTS, taking care to maintain hydration and pain relief. Peripheral vasodilatation and hypotension from epidurals may worsen PoTS; therefore, it is advisable to site epidurals in the left lateral position. There are case reports of successful vaginal delivery with continuous low dose epidural infusion and invasive blood pressure monitoring.[21] The Valsalva maneuver during the second stage can potentially worsen hemodynamic instability. In extreme situations, it may be advisable to limit second stage with instrumental delivery. This should be balanced against the risk of perineal injury.

For caesarean delivery, CSE (with a lower dose of anaesthetic in the spinal space) may be preferable to a single shot spinal injection as it is less likely to provoke sudden hemodynamic changes with emphasis on fluid preload and the use of phenylephrine to improve maternal cardiovascular stability. Women with PoTS should have an antenatal anaesthetic review with a documented plan for analgesia and anaesthesia in labour.

Postnatally, there is usually progressive improvement of symptoms to the pre-pregnancy state and there are no documented long-term implications of the effects of pregnancy on PoTS.

Management of hEDS patients in pregnancy

These women should ideally have a pre-pregnancy appointment to discuss the maternal complications and the risk of fetal inheritance of the condition. Current symptoms and previous pregnancy outcomes should be taken into consideration when formulating an individualized management plan. We recommend a multidisciplinary input including anaesthetists, rheumatologists, obstetrician and physician as appropriate. It would be reasonable to offer these women a cervical length scan. Antenatal anaesthetic review is mandatory to have plans for analgesia and choice of anaesthesia in labour and delivery.

Vaginal delivery should be aimed for where there are no obstetric contraindications, unless severe joint problems such as hip dislocation/subluxations preclude vaginal delivery. Increased possibility of short or precipitate labour with a risk of postpartum haemorrhage should be considered; measures should be in place to prevent postpartum haemorrhage. To prevent rupture of the perineum and perineal delivery, prompt episiotomy should be given when required. The perineum should be carefully assessed and repaired by an experienced person, bearing in mind the possibility of defective healing and extended unrecognized tears. It is important to have venous access and blood group and save done at onset of labour along with active management of third stage. Following a caesarean delivery, these patients will benefit from prophylactic oxytocin infusion and more aggressive approach in the event of postpartum haemorrhage.

Conclusion

Pregnancies in patients with JHS can be well tolerated and with good outcomes following delivery. Awareness of this condition will enable obstetric management plans to be made on an individualized basis with multi-disciplinary input to optimize maternal and neonatal outcomes.

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AK prepared the manuscript. NVR guided AK in writing the manuscript and proofread the final manuscript.

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